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## Description

The present invention is broadly directed to a device for the controlled release of an active substance into a fluid medium at a constant (i.e., zero-order) rate over an appreciable or prolonged time interval. Said device comprises said substance homogeneously disposed and contained the shape of a substantially truncated cone by means of an impermeable wall or coating on the base and side (but not the top) of said cone. When the device is a partially coated tablet, particularly a tablet comprising a pharmaceutically effective agent for oral use in a mammal, the present invention is also directed to a tablet press for use in the manufacture of a tablet in the shape of said substantially truncated cone, and (after fully coating such tablets by conventional means) to an apparatus for removal of the tablet coating from the top (i.e., smaller diameter end) of the tablets.

A readily manufactured device which will dependably release an active material (e.g., a pharmaceutical agent, a cleanser or a deodorizer) at a zero-order rate into a fluid medium (gaseous or liquid) has remained an elusive goal, particularly when the device is in the form of a tablet for controlled invivo release of a pharmaceutical agent into a biological fluid (e.g., the fluid of the gastrointestinal tract).

An early proposed method was that of Jacobs, U.S. Patent 3,113,076 (1963) in which the drug was combined in a suitable carrier and tablets obtained by an extrusion method. The principle was to form tablets with approximately equal outer and "inner" surfaces, the latter accessed by aperture(s). As the exterior surface is dissolved, the area decreases, while as the inner surface dissolves, the surface area increases. Absent diffusion effects respecting the interior surface, the total surface, and thus rate of solution, would remain relatively constant. In its simplest form, Jacobs' tablet is a cylinder achieving equal inner surface by a multiplicity of cylindrical holes which are parallel to the axis of the outer cylinder, and accessed by the multiple apertures at each end of the cylinder. A related, but more sophisticated device, which now takes into account diffusion effects with respect to the inner surfaces, is that of Brooke, U.S. Patent 3,851,648 (1974). Brooke discloses a cylindrical container, closed at the ends, with a cavity in the shape of a cylinder sector with the aperture in the form of a slot in the outer surface of cylinder (parallel to the axis of the cylinder), said slot at the apex of the cylinder sector cavity. See also Brooke et al., J. Pharm. Sci. 66, pp. 159-162 (1977). In practice, this device produces release rates which are initially high; Lipper et al., J. Pharm. Sci. 66, pp. 163-164 (1977). It is suggested that the device might be implanted into body cavities, but there is no suggestion for use of this device in the form of an ordinary tablet, or for a method of manufacturing such a tablet.

Langer et al., A.I.Ch.E. Symposium Series, No. 206, vol. 77, pp. 10-20 (1981) analyzed several geometries for approaching zero-order release kinetics; a slab (open in one of its major faces; a coated

half-cylinder with a parallel, half-cylinder opening in its flat face; and a coated hemisphere with a small, open concavity in the center of its flat face. Only the latter provides predicted release rates close to zero-order, although even here an initially faster release is predicted, a result shown in practice by Hsieh et al., J. Pharm. Sci. 72, pp. 17-22 (1983) for release of sodium salicylate. Hsieh et al. propose a method for fabrication of such hemispheric devices in tablet form by initially molding a mixture of the drug and polymeric carrier, inserting a stick or bead into the center of the flat face, coating and finally removing the stick or bead from the face to form the small concavity. Such a method is hardly amenable to high speed tablet manufacture. Even without such methods, major problems were encountered by Hsieh et al. in this fabrication method, both in the techniques of coating and in uniformly opening the cavity.

Various types of boluses, for the relatively long term release of an active agent in the rumen or reticulum of a ruminant mammal, based on designs similar to those for tablets as discussed above, are also found in the prior art. See, for example, Dresback, U.S. Patent 4,220,152 (1980), Cardinal, U.S. Patent 4,601,893 (1986) and Guerrero et al., U.K. Patent Appn. 2,077,103 (1980).

More recently, Lai et al., Abstract No. 133, A.Ph.A. Meeting, October 21-24, 1985, derived mathematical diffusional models for drug release from various geometries including "a hemisphere with a dimple-shaped releasing surface" (presumably as described above) and "a truncated cone and a tapered cylinder with central releasing hole". No actual or suggested preparation of such tablets is indicated, nor is any possible advantage suggested for the truncated cone over the coated hemisphere described above.

We have now discovered a device for the controlled release of active substance into a fluid medium at a substantially constant (i.e., zero-order) rate which comprises said substance homogeneously disposed, with or without one or more inert diluents, and contained in the shape of a substantially truncated cone by means of an impermeable wall or coating on the base and side of said truncated cone. In a first preferred embodiment, the truncated cone has top to bottom (base) diameters in a ratio of 1:2 to 1:4 and a height to base diameter in a ratio of 1:1 to 1:4. In a second preferred embodiment, the cone has a convex base, which minimizes any tailing effect in which there is slower release of the active product at the end of the release period. Optionally the sides of the cone, when viewed in cross-section, are concave in shape. The expression "substantially truncated cone" is intended to encompass not only a true truncated cone (alternatively called the frustum of a cone), but variants possessing said convex base, said concave sides, a small disc or flat cylindrical section at the base of the cone, and/or an oval or polygonal cross-section in place of the circular cross-section of the cone. The term "fluid" is intended to encompass either liquid or gaseous media. The expression "impermeable wall or coating" encompasses any material which prevents

any substantial movement of the contents or of the surrounding fluid across the wall or coating.

Preferred embodiments of the present invention include a device wherein the substance or substances released are biologically active, such as an odor reducing, antimicrobial (germicidal) or pharmaceutical substance.

In one of its more preferred embodiment, the device is a tablet for oral administration to a mammal, which releases a pharmaceutically active substance into the fluid of the gastrointestinal tract of said mammal at a constant rate over an appreciable time interval. Such pharmaceutically active substances include, analgesics, anorexics, anthelmintics, antibacterials, antifungals, antidepressants, antihypertensives, bronchodilators, immunosuppressants, antilinflammatories and blood glucose lowering agents. The active substance is usually combined with inert ingredients, to aid in tablet formation, and/or in controlling the rate of release of said active ingredient. For example, the excipients will permit high speed tabletting by means of a tablet press which has been modified with an upper punch having a cavity which is in the shape of a substantially truncated cone, also a part of the present invention. Such tablets are coated with a material impermeable to the tablet contents and to gastrointestinal fluids, using methods well known in the art. Finally, the impermeable coating is removed from the top of each cone shaped tablet, employing special apparatus which is also part of the present invention.

The inert ingredients employed in tablets can be of the dissolution type (i.e., eroding and generally dissolving at the same time as the active ingredient), or they can form a matrix which is not soluble, and retains its shape as the active ingredient dissolves. When the inert ingredients are of the dissolution type, the coating should be relatively rigid so as to retain its shape as the tablet contents dissolve away into the fluid of the gastrointestinal tract.

In its most preferred embodiments, the present invention is directed to tablets in which the pharmaceutically active substance is an antihypertensive (particularly prazosin, trimazosin or doxazosin), an antianxiety agent (particularly hydroxyzine), a bronchodilator (particularly pирbutерол) or a blood glucose lowering agent (particularly глипизид).

In another more preferred embodiment, the present invention is directed to a bolus for retention in the rumen or reticulum (i.e., the rumeno-reticular sac) in longer term treatment of ruminants. The bolus is of a weight or shape so as to be retained in the rumen for at least two weeks, and so as to be readily administered by means of a conventional bolting gun.

Representative of the drugs which can be used individually or in combination in the bolus devices described herein are the following: anthelmintics, including morantel, pyrantel, oxantel, piperazine, diethylcarbamazine, levamisole, tetramisole, and hymenomycin B; antibacterials including sulfa drugs such as sulfanilamide, sulfathiazole, sulfamethazine, sulfaguanidine, and sulfapyridine; tetracy-

clines, such as 5-oxytetracycline, chlorotetracycline, doxycycline and Mannich bases thereof; penicillins such as ampicillin, penicillin G; aminoglycosides such as neomycin, streptomycin, apramycin, bacitracin as its zinc or methyl disalicylic acid derivative; macrolides such as erythromycin, oleandomycin and tylosin; antibacterial growth promotants such as avoparcin, polymyxin, lincomycin, bambermycin and efrotomycin; hormonal growth promotants including diethylstilbestrol, zearalanol and melengestrol acetate; antiparasitic agents such as amprollium; nutritional agents such as salts of magnesium, selenium, copper and vitamins such as thiamine hydrochloride; molluscicides such as N-tritylmorphine; and bloat prevention agents such as alcohol ethoxylates and poly(oxyethylene)-poly(oxypropylene)-poly(oxyethylene)polymers, e.g. poloxalene.

Figure 1 shows in cross-section a view of a tablet of the present invention, prepared on a conventional tabletting machine using the punches of the present invention, then coated and the coating at the top of the cone removed by means of the coating removal apparatus of the present invention.

Figure 2 shows in perspective a segment of a flat cylindrical container with a cavity in the shape of a substantially truncated cone, having a convex base and a circular aperture in the top circular face of the cylinder which is also the top of said cavity. When the device is a tablet, the container is formed by high speed compression coating of a preformed tablet in the shape of a truncated cone. When the device is a bolus such a container can be filled by injecting the active ingredient in melted form.

Figure 3 represents a perspective view of Figure 1.

Figure 4 illustrates in cross-section a tablet or container of the present invention with preferred convex base and optional concave sides.

Figure 5 illustrates the unconventional upper punch, and conventional lower punch and die used in a conventional tablet press for the manufacture of uncoated tablet cores in the shape of a truncated cone.

Figure 6 shows in cross-section a side view and Figure 7 a view from above of apparatus useful in removing the coating from the top (smaller diameter end) of conventionally coated tablets which are in the shape of a truncated cone.

Figures 8 and 9 show in side and top views an alternative form of the apparatus useful for removing the top coating from tablets.

Figure 10 illustrates in perspective a bolus of the present invention. Figure 11 illustrates in cross-section a back to back pair of flat cylinders or discs which are mounted in a carrier to form the bolus of Figure 10.

Figures 12-16 show the rate of release of active ingredient from tablets prepared in specific Examples below.

The present invention is readily practiced, offering advantages over controlled release devices previously available. One advantage is the nearly

constant (zero order) rate of release of active ingredient over virtually the entire release period, particularly when the base of the present truncated cone is convex in shape. Another advantage is the ease of manufacture, particularly in the case of tablets containing pharmaceutically active agents for use in mammals, where the present invention further provides apparatus useful in the manufacture of such tablets.

When the device is macro in nature, such as a device for slow release of a deodorizer into a room or of an antimicrobial agent and/or a deodorizer into a toilet tank, the wall can be constructed as a container from standard construction materials, such as a moldable plastic, using methods standard in the art. The preconstructed container can then be filled with the active agent, usually in an inert carrier. Such a device is illustrated in Figure 4, in cross-section, having an impermeable wall 41 on the convex bottom 44 and concave side 43, access of the contents to the fluid environment at the top 42 of the truncated cone, and contents in the shape of a substantially truncated cone.

When the present device is a tablet, ordinary cylindrical or drum shaped tablets containing the desired active ingredient and excipients can be formed on a conventional tablet press, then ground or filed to produce tablets of the desired truncated cone shape, hand coated and the coating removed from the top of the truncated cone with a razor blade. However, the present invention further provides apparatus for the much more highly efficient manufacture of such tablets.

In said efficient manufacturing process, uncoated tablets are initially formed in the desired shape of a truncated cone on a single or multistation tablet press which is conventional except for the use of an upper punch having a cavity substantially in the shape of a truncated cone. Figure 5 illustrates in cross-section such an unconventional upper punch 51 having a cavity 54 in the shape of a truncated cone, used in conjunction with a conventional die 52 and lower punch 53 which can be flat or preferably convex, as shown.

Figure 1, representing a finished tablet, can also be used to illustrate the shape of the present punches and die. Thus, in cross-section, the face of the upper punch is represented by a line connecting points CBAHGF, with the cavity designated as 1, while the face of the lower punch in convex form (cavity designated as 3) is represented by the curved line DE. The inside diameter of the die is the straight line DE (or CF), matching the outside diameter of each punch. The punches and die are conventionally manufactured to the desired specifications.

Although powders of active compounds having appropriate physical properties can be tabletted without excipients, the active compound will generally be thoroughly blended with conventional, pharmaceutically acceptable tablet excipients to form either tablets of the dissolution type (where the excipient disintegrates and generally dissolves along with the active ingredient) or of the matrix type (where the active ingredient diffuses into the surrounding medium leaving the matrix intact). Excipients typically

used for either purpose are exemplified below.

Since in standard operation of the tablet press, the upper and lower punches do not touch one another, and each punch will generally have a small flat area at its outer edge, the tablets formed in this manner necessarily possess a flat cylinder or disc shaped central portion, designated as 2 in Figure 1 and 33 in Figure 3. The thickness (CD/DF in Figure 1) of this disc shaped portion can be minimized, e.g., to as little as 0.02 to 0.04 inches (0.05 to 0.102 cm), but even if it is relatively thick, e.g. even up to one quarter of the height of the truncated cone, it will not have a significantly adverse effect on the desired zero-order rate of release of the active ingredient.

Once formed the tablets are optionally compression coated by conventional methods (see Ellis et al., Chapter 10, "Tablet Coating", in "The Theory and Practice of Industrial Pharmacy", Lachman et al., eds., Lea and Febiger, 1970, p. 207 et seq.) to form cylindrical or drum shaped tablets, as illustrated in Figure 2, where, in segmented perspective, 10 represents the original truncated cone shaped tablet, having a convex base 13 and containing the active ingredient and drug release surface accessing the environment at 12, and the vertically cross-hatched portion refers to the added compression coating 11 having an over-all cylindrical shape.

However, it is preferred at this stage to coat the tablets using conventional methods and materials. See Ellis et al., loc. cit. The coating materials which are used are substantially impermeable to the tablet contents and to the ultimate gastrointestinal fluid. Such conventional materials include aqueous dispersions of ethyl cellulose (e.g. Aquacoats sold by FMC Corp.) which are sprayed onto the tablets and the coating dried in conventional coating pans. On an experimental scale, coating is conveniently accomplished by repeated dipping of the tablet in a volatile organic solution of a polymer such as ethylene-vinyl acetate copolymer and drying. Methylene chloride or toluene are the preferred solvents when the tablet coating is an ethylene-vinyl acetate copolymer.

The last stage in the manufacture of present partially coated tablets employs further unconventional apparatus, whose purpose is to remove the impermeable coating from the top (or small end) of the truncated cone, so as to permit ultimate access of the tablet contents to intestinal fluid. Two views of such apparatus, particularly useful for the manufacture of experimental quantities of tablets of the present type, are illustrated in Figures 6 and 7, in side and top views, respectively. Tablets 63 are seated in corresponding perforations 73 in the movable plate 61/71. The perforations are also in the shape of truncated cone which is substantially equangular with the truncated cone of the tablets, but of lesser height. The larger top diameter of the perforations is usually similar to, but not larger than the diameter and the large end of the tablets. The smaller diameter at the bottom of the perforations is larger than the diameter at the small end of the tablets, such that at least some portion of the seated tablets will be below the plane of the plate.

As the plate 61/ 71 is moved from right to left in Figure 6 and 7, the tablets 63 move under and are held in place by the support means 62/ 72 as they move over the grinding means 64/ 74 (e.g. a rotary cutting wheel or grinder rotated by a motor 65/ 75), adjusted so as to remove the coating from the smaller end of each tablet. As the finished tablets move further to the right, they are ejected from the plate.

Apparatus for larger scale operation is illustrated in Figures 8 and 9, side and top views, respectively. The tablets are held in like perforations in a circular plate 82/ 95 rotated by an attached variable speed motor 86. The tablets are seated into the like shaped perforations in one segment of the circular plate by vibrational means, e.g., a vibrating bowl feeder 83/ 92. The support means 84 will permit only those tablets which are seated to move, by rotation of the plate, into the stationary grinding station, comprising a cutter wheel or grinder 85/ 93 and attached variable speed motor 86/ 94. Waste powder is collected in a bin 87 below the grinding means. Once finished, the tablets will be ejected in the next segment, e.g., by a combination of a sloping stationary plate mounted below the moving plate which unseats the tablets and a stationary gate, perpendicular to the moving plate and mounted at an angle which sweeps the dismounted, finished tablets into a receptacle; or by an air ejector means 88/ 91 such that the tablets exit via chute 81 to a receptacle 89.

In order to more dependably achieve a substantially constant tablet to tablet uncoated release area, concave sided tablets or slight tapering of the side at the top the truncated cone of the fully coated tablets prior to removal of the top coating by machine. In this way, any slight tablet to tablet variation in the depth of cut will lead to insignificant variation in the release area.

Finished tablets prepared in this manner are illustrated by Figures 1, 3 and 4. Figures 1 and 3 represent a tablet in the form of a truncated cone having a convex base and a small cylindrical section or disc at the base of the cone and a convex base. In Figure 1, the cross sectional area 1 is the portion of the tablet formed by the upper punch, 2 is the flat disc formed by the die, 3 is the convex base portion formed by the lower punch, 4 is the impermeable coating and 5 is the tablet face from which the coating has been removed. Figure 3 shows a like tablet in perspective. The tablet coating has been removed from the face 31. The volume 32 is the portion of the tablet formed by the upper punch, 33 is the flat disc formed by the die, and 34 is the convex base formed by the lower punch. Figure 4 illustrates an alternative embodiment of the tablet in cross section, having coating 41, coating free surface 42, concave shaped side 43 and convex base 44.

The finished tablets are tested *in vitro* for zero order release of the active ingredient as detailed in the Examples below. The *in vitro* tests are correlated with the *in vivo* rate of release, for example, by measuring the blood levels of an active agent over time following ingestion of the tablet.

When the present device is used for delivery of active agent(s) to a ruminant mammal it will generally

be in the form of a bolus for long term delivery (e.g., 2 weeks or more) in the rumeno-reticular sac (rumen or reticulum) of a ruminant animal, dosed orally by means of a conventional bolting gun. The bolus is designed so that it is of a size that will permit introduction into the rumeno-reticular sac via the esophagus, and retained there by means of its weight, or by means of a change in shape which occurs after its administration.

5 In the present instance, it is convenient to prepare discs or drums containing a cavity substantially in the shape of a truncated cone with ultimate access to the rumeno-reticular environment at the top of a cone as a circular opening in the face of the drum or disc. The active ingredients are homogeneously blended with a meltable polymer powder (for example, the biodegradable p-dioxanone or 65/35 lactide glycolide copolymer of U.K. Patent 2,077,103), the blend melted and injection molded in the desired truncated cone shape. As shown in Figure 11, the molded drug containing cones are then mounted by means of an adhesive 113 into a cylindrical shaped holder 111, conveniently constructed of moldable plastic, so as to have on opposite faces drug release surfaces 112. Alternatively, preformed discs having a cavity in the shape of a truncated cone, e.g., as illustrated in Figure 2, are injected with the drug in a meltable polymer, and after cooling and solidification, glued back to back to form a cylinder similar to that shown in Figure 11 with like drug release surfaces 112 on opposite faces. As shown in Figure 10, the cylinders or "double discs" 104 having drug release surfaces 102 on opposite faces are mounted into a rack 101 conveniently constructed of moldable plastic or metal. The cylinders are spaced in a manner which permits access of the mixture of active ingredient(s) and polymer to the ultimate rumeno-reticular environment. The rack and mounted discs form an elongated cylinder well suited for introduction into the rumeno-reticular sac by means of a bolting gun. The drug release surfaces 112 at each end of the elongated cylinder access the environment directly, and two such surfaces access each space within the elongated cylinder. When the rack is of plastic construction, a rectangular flap 103 is permanently attached by snaps or by means of a water insoluble glue along its edge AB. The rectangular flap, constructed of an insoluble, flexible and resilient material is wrapped in rolled configuration around the elongated cylinder, constrained in that configuration by a constraining means, e.g., attached on the opposite edge CD of the rectangular flap edge with a water soluble glue, e.g., gelatin or a starch or cellulose based paste. Once orally injected into the rumen or reticulum, the constraining means dissolves, releasing the flap at the edge CD. The resilient flap then unrolls to provide a substantially flat flap 103 as illustrated, the whole providing a geometric shape and size which retains the device within the rumeno-reticular sac. The flap is suitably constructed of polyethylene or of a thermoplastic elastomer such as a styrene/elastomer block copolymer, or polyurethane and polyester/polyether block copolymers (see "Modern Plastics Encyclopedia 1985-1986, pp. 97-

99). Alternatively, the rack is constructed of metal or ceramic so as to have sufficient weight to be retained in the rumeno-reticular sac by means of gravity, without need for a releasable flap.

The following examples are given by way of illustration and are not to be construed as limitations of this invention, many variations of which are possible within the scope and spirit thereof.

#### EXAMPLE 1

##### Dissolution Type Tablets of Sodium Benzoate

Powders of sodium benzoate (30 parts by weight), spray dried lactose (69.5 parts by weight) and magnesium stearate (0.5 parts by weight) were thoroughly blended. By compression means, the blend was compressed into ordinary flat cylindrical tablets having a height of 0.17 inches (0.432 cm) and a diameter of 0.41 inches (1.041 cm). Using an ordinary file, the tablets were filed down into the shape of truncated cones, retaining the original height and base dimensions. In this manner, two sizes of tablets were prepared, one having a 0.2 inch top diameter (a top:bottom ratio of 1:2) and weighing 0.34 g., and the other having a 0.14 inch (0.356 cm) top diameter (a top:bottom ratio of 1:3) and weighing 0.30 g. The tablets were hand coated by repeated dipping of a portion of the tablet into a 10% methylene chloride solution of ethylene-vinyl acetate copolymer (Elvax® 40, DuPont, 40% vinyl acetate) and drying. In this case a total of 3 coats were applied to all portions of each tablet. The cross section of coating at the top of each tablet was removed with a razor blade.

To test the rate of dissolution, simulated intestinal fluid was prepared by dissolving  $\text{KH}_2\text{PO}_4$  (13.6 g.) in 1800 ml.  $\text{H}_2\text{O}$ , adjusting the pH to 7.5 with about 16 ml of 5N NaOH, and finally diluting to 2 l. with  $\text{H}_2\text{O}$ . The fluid (110 ml.) was measured into each of six 100 ml., clear glass, Wheaton vials. One tablet was added to each vial. The vials were stoppered and held on a laboratory shaker with rubber bands. The vials were rotated at 8 rpm at 24°C. At 0.5 hour intervals, 1 ml. samples were withdrawn from each vial, and replaced with 1 ml. fresh simulated intestinal fluid. At the same time, depletion geometry was monitored by examining individual tablets. The tablet contents gradually eroded from top to the base of the tablet over 6 hours. The results of the present dissolution study with tablets having a 1:2 top:bottom ratio are shown in Figure 12. The results with the 1:3 top:bottom ratio tablets are shown in Figure 13.

#### EXAMPLE 2

##### Matrix Type Tablets of Sodium Benzoate

##### Method A

Powders of sodium benzoate (30 parts by weight), ethyl cellulose (40 parts by weight), spray dried lactose (29.5 parts by weight) and magnesium stearate (0.5 parts by weight) were thoroughly

blended. By the methods of the preceding Example, like tablets were prepared.

These tablets were tested for rate of dissolution by the method of the preceding Example. Since these tablets were of the matrix type, no erosion of the tablet contents was evident as the sodium benzoate dissolved. The results obtained with present matrix tablets of 1:2 top:bottom ratio are shown in Figure 14. The results with 1:3 top:bottom ratio are shown in Figure 15.

##### Method B

Powders of sodium benzoate (13.80 g., 30 parts by weight), ethyl cellulose (18.40 g., 40 parts by weight), spray dried lactose (12.90 g., 28 parts by weight) were combined in a 250 ml. amber bottle and blended by tumbling for 10 minutes on a Fisher-Kendall mixer. The blend was screened through a U.S.S. Screen #40 sieve and reblended for 5 minutes. Then magnesium stearate (0.90 g., 2 parts by weight) was added and the mixture blended for an additional 5 minutes. The resulting blend was compressed into tablets on a conventional single punch tablet press (Manesty, Model F3) in manual mode, using a specially designed upper punch with truncated cone cavity (as illustrated in Figure 5, with dimensions corresponding to those of the resulting tablet, as noted below), a conventional die and a conventional round concave lower punch. The average weight of the resulting tablets was 362 mg., containing 108 mg. of sodium benzoate. The tablet dimensions were: top diameter, 0.135 inches (0.343 cm); bottom diameter 0.41 inches (1.041 cm); over-all height, about 0.23 inches (0.102 cm); the flat, cylindrical portion at the base of the truncated cone was 0.04 inches thick. The tablets were readily handled; they were not friable, having a more than acceptable range of tablet hardness ( $K_p=7.5$ ) when conventionally measured on a Heberlin Hardness Tester. The tablets were coated according to the method of Example 1, except that a toluene was used as the solvent for the copolymer. The coating was removed from the smaller, flat end of the truncated cone by manual operation of the apparatus shown in Figures 6 and 7.

The dissolution of the resulting tablets was studied by the rotating basket method (50 rpm) at 37°C. in 0.01M phosphate buffer at pH 3, otherwise according to the method detailed in Example 1. The results are shown in Figure 16.

#### EXAMPLE 3

##### Trimazosin Tablets

Trimazosin hydrochloride monohydrate (15.50 g., equivalent to 13.80 g. of anhydrous free base), lactose (11.14 g.), ethyl cellulose (18.40 g.) and magnesium stearate (0.90 g.) were blended and formed into tablets according to the preceding Example. The tablets weighed 320 mg., containing 96 mg. of trimazosin (free base) activity. They showed an acceptable range of tablet hardness (8-8.5), and were of substantially identical dimensions to those of the

preceding Example, except that the thickness of the flat cylinder at the base of the truncated cone was 0.03 inches (0.076 cm). The tablets were coated and the flat top removed in the same manner as in the preceding Example.

#### EXAMPLE 4

##### Sertraline Tablets

Sertraline HCl (antidepressant, (+)-*cis*-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methylnaphthlamine; 15.50 g., equivalent to 13.80 g. of free base) and like quantities of the same excipients were converted to tablets according to the preceding Example. The tablets were of like dimensions, except that the disc shaped portion at the base of the truncated cone was 0.05 inches (0.127 cm) thick. Tablet hardness was acceptable (8.4). The weight of the tablets was 420 mg., corresponding to 126 mg. of sertraline (free base activity).

Controlled release tablets containing the desired activity level of prazosin, doxazosin, hydroxyzine, pibuterol and glipizide are prepared in like manner.

#### EXAMPLE 5

##### Morantel Tartrate Bolus

Powders of morantel tartrate and ethylene vinyl acetate copolymer are blended in the proportion of 55:45 by weight. Suitable copolymer designated MU-760 is available from U.S. Industrial Chemical Co. by injection molding, this mixture is formed into the shape of truncated cones having a convex base, with top diameter 0.23 inch (5.08 cm), base diameter 0.7 inch (1.77 cm) and height 0.41 inch. As illustrated in Figure 11, each cone is fitted and glued into a flat cylinder or disc (premolded of polyethylene) having a like shaped cavity, and each pair of discs is glued back to back. Five pairs of discs are mounted into a polyethylene rack as shown in Figure 10, with 0.3 inch (13.46 cm) space between each pair of discs. The overall length of the cylindrical rack is 5.3 inches (13.46 cm) and the diameter 1 inch. A rectangular flap, 5.3 (13.46) x 4 (10.16) cm inches with rounded corners, is cut from 0.03 inch (0.076 cm) thick high density polyethylene sheet and attached by a 5.3 inch (13.46cm) side with water insoluble glue to the cylindrical rack, as shown in Figure 10. Finally, the flap is wrapped around the cylindrical rack and attached along the other 5.3 side by a tape having a water soluble adhesive. The bolus contains 4 g. morantel base activity.

In like manner, triple sulfa bolus are prepared by substituting the morantel tartrate with 18 parts by weight of sulfamethazine, 18 parts by weight of sulfamerazine and 18 parts by weight of sulfathiazole.

#### EXAMPLE 6

##### Diaper Pail Deodorant

A cylindrical container, substantially as illustrated in Figure 2, having an outside diameter of 3 inch-

es (7.62 cm) and a height of 2 inches (5.08 cm), and truncated cone shaped cavity with 0.8 inch diameter opening at the top, 2.3 inch (5.08 cm) diameter base and height of 1.4 inches (3.55 cm), is constructed of polyethylene by injection molding. A mixture of *p*-dichlorobenzene and polyethylene glycol (average molecular weight, 1000) in 60:40 portions by weight is melted by warming. The container is filled with the melt, which solidifies on cooling to room temperature, and sealed with paper. The latter is removed prior to use as a deodorant in the air space of a diaper pail, where it is effective for at least several days to 2 weeks or more.

#### EXAMPLE 7

##### Toilet Tank Germicide

The polyethylene container of the preceding Example is filled with a melted mixture of germicidal *p*-phenylphenol and *p*-dioxanone in 1:10 ratio by weight. The filled container is cooled and sealed with paper. The paper is removed just prior to use in a toilet tank where it provides effective germicidal action for several weeks under typical use conditions.

#### Claims

1. A device for the controlled release of one or more active substances into a fluid medium which comprises said substance homogeneously disposed, with or without one or more inert diluents, and contained in the shape of a substantially truncated cone by means of an impermeable wall or coating on the base and side of said truncated cone.
2. A device of claim 1 wherein the ratio of the diameters of the top to the base of the truncated cone is in the range of 1:2 to 1:4, and the ratio of the height to the diameter of the base is in the range of 1:1 to 1:4.
3. A device of claims 1 or 2 wherein the truncated cone has a convex base.
4. A device of any preceding claim wherein the truncated cone has a concave side.
5. A device of any preceding claim wherein the substance is biologically active.
6. A device of any preceding claim wherein the activity is germicidal, pharmaceutical or prevents or reduces odors in or emanating from the fluid medium.
7. A bolus for oral administration into the reticulum or rumen of a ruminant mammal, said bolus being retained in said rumen or reticulum and releasing one or more active agents into the environment of said rumen or reticulum at a substantially constant rate over a prolonged period of time, which comprises one or more devices as claimed in any preceding claim said active agent or agents homogeneously disposed in a matrix and contained in the shape of one or a plurality of substantially truncated cones by means of an impermeable wall on the base and side of said truncated cone or cones.
8. A bolus of claim 7 having said active agent contained in a plurality of truncated cone shaped cavities in a plurality of flat cylinders or discs

mounted in a carrier of elongated cylindrical shape and spaced to permit of access of the top of said truncated cones to said environment of the rumen or reticulum, said carrier having an attached flexible and resilient flap capable of constraint in rolled configuration around said elongated cylinder by a constraining means which releases said flap once in the environment of the reticulum or rumen.

9. A bolus of claim 8 wherein the active agent is morantel or a pharmaceutically acceptable salt thereof in a polymer matrix.

10. A tablet for oral administration to a mammal which releases a pharmaceutically active substance into the fluid of the gastrointestinal tract of said mammal at a constant rate over an appreciable time interval which comprises a device as claimed in any one of claims 1 to 6 said substance homogeneously disposed, with or without one or more pharmaceutically-acceptable diluents, and contained, in the shape of a substantially truncated cone, by means of an impermeable coating or wall on the base and side of said truncated cone.

11. A tablet of claim 10 in which said substance is contained by means of coating.

12. A tablet of claim 10 or 11 wherein the substance is an antihypertensive, an antianxiety agent, a bronchodilator or a blood-glucose lowering agent.

13. A tablet of claims 10 to 12 wherein the substance is prazosin, trimazosin, doxazosin, hydroxyzine, sertraline, pirlbuterol or glipizide.

14. A single-station or multistation tablet press for use in the manufacture of tablets in the shape of a substantially truncated cone which, at each station, comprises

- (a) a conventional, round and flat or convex lower punch;
- (b) a conventional, round die; and
- (c) a corresponding upper punch having a cavity which is in the shape of a substantially truncated cone.

15. A tablet press of claim 14 wherein the side of the cone shaped cavity is concave in shape.

16. A tablet press of any one of claims 14 to 15 wherein the ratio of the diameters of the top and the base of said truncated cone is in the range of 1:2 to 1:4 and the ratio of the height to the diameter of the base is in the range of 1:1 to 1:4.

17. An apparatus for removing the coating from the smaller diameter end of a fully coated tablet which is substantially in the shape of a first substantially truncated cone, which comprises

- (a) a moving, horizontal plate containing a plurality of perforations in the shape of a second equiangular truncated cone of lesser height, having its larger diameter at the top of the plate and no larger than the larger diameter of said first truncated cone, and its smaller diameter at the bottom of the plate and larger than the smaller diameter of said first truncated cone;
- (b) a means for seating said fully coated tablets in said perforations;
- (c) a stationary support means above said moving plate to hold the seated tablets in place;
- (d) a stationary grinding means below the plane of said plate spaced so as to remove the coating

from the smaller diameter end of said supported tablets;

- (e) a means of ejecting the finished tablets.

18. A process for the preparation of a tablet of claim 10 which comprises the steps of:

- (a) forming uncoated tablets in the shape of a substantially truncated cone in a single-station or multistation tablet press comprising a conventional, round and flat or convex lower punch; a conventional, corresponding round central die; and a corresponding upper punch having a cavity which is in the shape of a substantially truncated cone;
- (b) fully coating said uncoated tablets with an impermeable coating by conventional means;
- (c) removing the coating from the smaller diameter end of the fully coated tablets by means of apparatus comprising a moving horizontal plate having perforations of a shape and size to seat said tablets with the smaller end below the plane of the plate; a means for seating said fully coated tablets in said perforations; a stationary support means above said moving plate to hold said tablets in place; a stationary grinding means below the plane of said plate spaced so as to remove the coating from the smaller diameter end of the fully coated tablets; and a means for ejecting the finished tablets.

19. A process of claim 18 wherein in step (a) the lower punch is convex.

#### Patentansprüche

1. Einrichtung für die kontrollierte Freigabe einer oder mehrerer aktiver Substanzen in ein fluides Medium hinein, welche diese Substanz homogen verteilt, mit oder ohne ein oder mehrere inerte(s) Verdünnungsmittel, und in Form eines im wesentlichen stumpfen Kegels gehalten enthält, und zwar mittels einer undurchlässigen Wandung oder Beschichtung auf der Basis und den Seiten dieses Kegelstumpfs.

2. Einrichtung nach Anspruch 1, worin das Verhältnis der Durchmesser vom oberen Ende zur Basis des Kegelstumpfs im Bereich von 1:2 bis 1:4 liegt und das Verhältnis der Höhe zum Durchmesser der Basis im Bereich von 1:1 bis 1:4 liegt.

3. Einrichtung nach den Ansprüchen 1 oder 2, worin der Kegelstumpf eine konvexe Basis aufweist.

4. Einrichtung nach irgendeinem vorhergehenden Anspruch, worin der Kegelstumpf eine konkave Seite aufweist.

5. Einrichtung nach irgendeinem vorhergehenden Anspruch, worin die Substanz biologisch aktiv ist.

6. Einrichtung nach irgendeinem vorhergehenden Anspruch, worin die Aktivität germizid oder pharmazeutisch ist oder Gerüche verhindert oder vermindert, die in oder aus dem fluiden Medium freigesetzt werden.

7. Bolus für die orale Verabreichung in den Netzmagen oder den Pansen eines wiederkäuenden Säugers, wobei der Bolus im Pansen oder Netzmagen zurückgehalten wird und ein oder mehrere aktive(s) Mittel mit einer im wesentlichen konstanten Geschwindigkeit über einen längeren Zeitraum in die

Umgebung des Pansens oder Netzmagens freisetzt und der eine oder mehrere Einrichtungen nach irgendeinem vorhergehenden Anspruch umfaßt, wobei das bzw. die aktive(n) Mittel homogen in einer Matrix verteilt und in Form eines oder einer Vielzahl von im wesentlichen stumpfen Kegels(n) enthalten ist, und zwar mittels einer undurchlässigen Wandung auf der Basis und den Seiten dieses Kegelstumpfes oder dieser Kegelstümpfe.

8. Bolus nach Anspruch 7, der das aktive Mittel in einer Vielzahl von Hohlräumen in Form eines Kegelstumpfes in einer Vielzahl flacher Zylinder oder Scheiben enthält, welche in einem Trägergestell länglicher zylindrischer Form montiert und in einem Abstand angebracht sind, um der Oberseite der Kegelstümpfe Zugang zur Umgebung des Pansens oder Netzmagens zu gewähren, wobei das Trägergestell eine daran befestigte flexible und elastische Manschette aufweist, die in gerollten Zustand um den länglichen Zylinder mittels einer Haftvorrichtung gehalten werden kann, die diese Manschette, nachdem sie sich in der Umgebung des Netzmagens oder Pansens befindet, ablöst.

9. Bolus nach Anspruch 8, worin das aktive Mittel Morantel oder ein pharmazeutisch annehmbares Salz desselben in einer Polymermatrix ist.

10. Tablette zur oralen Verabreichung an einen Säuger, die eine pharmazeutisch aktive Substanz bei konstanter Geschwindigkeit über einen deutlichen Zeitraum in die Flüssigkeit des Gastrointestinaltraktes dieses Säugers freisetzt und eine Einrichtung nach irgendeinem der Ansprüche 1 bis 6 umfaßt, wobei die Substanz, mit oder ohne ein oder mehrere pharmazeutisch annehmbare(s) Verdünnungsmittel, homogen verteilt und mittels einer undurchlässigen Beschichtung oder Wand an der Basis und den Seiten dieses Kegelstumpfes in Form eines im wesentlichen stumpfen Kegels gehalten enthalten ist.

11. Tablette nach Anspruch 10, in welcher die Substanz mittels einer Beschichtung enthalten ist.

12. Tablette nach Anspruch 10 oder 11, worin die Substanz ein Antihypertensivum, ein Mittel gegen Angstzustände, ein Bronchodilator oder ein Blutzucker senkendes Mittel ist.

13. Tablette nach den Ansprüchen 10 bis 12, worin die Substanz Prazosin, Trimazosin, Doxazosin, Hydroxyzin, Sertralin, Pirbuterol oder Glipizid ist.

14. Einstempelige oder Rundläufer-Tablettenpresse für die Verwendung bei der Herstellung von Tabletten in Form eines im wesentlichen stumpfen Kegels, welche an jedem Platz

- (a) einen üblichen runden und ebenen oder konvexen unteren Stempel,
- (b) eine übliche runde Matrize und
- (c) einen entsprechenden oberen Stempel mit einer Höhlung, die die Form eines im wesentlichen stumpfen Kegels hat, enthält.

15. Tablettenpresse nach Anspruch 14, worin die Seite der kegelförmigen Höhlung von konkaver Form ist.

16. Tablettenpresse nach irgendeinem der Ansprüche 14 bis 15, worin das Verhältnis der Durchmesser vom oberen End und der Basis des Kegel-

stumpfes im Bereich von 1:2 bis 1:4 und das Verhältnis der Höhe zum Durchmesser der Basis im Bereich von 1:1 bis 1:4 liegt.

17. Vorrichtung zur Entfernung der Beschichtung vom Ende mit dem kleineren Durchmesser einer vollständig überzogenen Tablette, die die Form eines ersten, im wesentlichen stumpfen Kegels hat, welche

5 (a) eine bewegliche, horizontale Platte, die eine Vielzahl von Perforationen enthält, die in Form eines im wesentlichen stumpfen zweiten Kegels mit gleichen Winkeln von geringerer Höhe vorliegen, dessen größerer Durchmesser sich an der Oberseite der Platte befindet und der nicht größer als der größere Durchmesser des ersten Kegelstumpfes ist und dessen kleinerer Durchmesser sich am Boden der Platte befindet und größer als der kleinere Durchmesser des ersten Kegelstumpfes ist;

10 (b) Mittel zum Einsetzen der vollständig überzogenen Tabletten in die Perforationen,

(c) eine stationäre Schleifeinrichtung oberhalb der beweglichen Platte, um die eingesetzten Tabletten an ihren Plätzen zu halten,

15 (d) eine stationäre Schleifeinrichtung unterhalb der Ebene der Platte, die in einer solchen Entfernung angeordnet ist, daß sie die Beschichtung von dem Ende der gehaltenen Tabletten, das den geringeren Durchmesser besitzt, entfernt,

20 (e) ein Mittel zum Auswurf der fertigen Tabletten umfaßt.

18. Verfahren zur Herstellung einer Tablette gemäß Anspruch 10, welches die Schritte:

25 (a) Formen unbeschichteter Tabletten in Form eines im wesentlichen stumpfen Kegels in einer einstempeligen oder Rundläufer-Tablettenpresse, die einen üblichen runden und ebenen oder konvexen unteren Stempel, eine übliche entsprechende runde zentrale Matrize und einen entsprechenden unteren Stempel mit einer Höhlung, die in Form eines im wesentlichen stumpfen Kegels vorliegt, aufweist,

(b) vollständiges Überziehen der unbeschichteten Tabletten mit einer undurchlässigen Beschichtung auf übliche Weise,

30 (c) Entfernen der Beschichtung von dem Ende der vollständig überzogenen Tabletten, das den kleineren Durchmesser besitzt, mittels einer Einrichtung, die eine bewegliche, horizontale Platte mit Perforationen in einer solchen Form und Größe, daß sich die Tabletten mit dem schmaleren Ende unterhalb der Ebene der Platte anordnen, Mittel zum Einsetzen der vollständig überzogenen Tabletten in diese Perforationen, eine stationäre Hafteinrichtung oberhalb der beweglichen Platte, um die eingesetzten Tabletten an ihren Plätzen zu halten, eine stationäre Schleifeinrichtung unterhalb der Ebene der Platte, die in einer solchen Entfernung angeordnet ist, daß sie die Beschichtung von dem Ende der vollständig beschichteten Tabletten, das den geringeren Durchmesser besitzt, entfernt, und Mittel zum Ausgeben der fertigen Tabletten aufweist, umfaßt.

35 19. Verfahren nach Anspruch 18, worin in Stufe

40 (a) der untere Stempel konvex ist.

### Revendications

1. Dispositif pour la libération contrôlée d'une ou plusieurs substances actives dans un milieu fluide, qui comprend ladite substance répartie de manière homogène, avec ou sans un ou plusieurs diluants inertes, et présente sous forme d'un cône nettement tronqué au moyen d'une paroi ou d'un revêtement imperméable sur la base et le côté dudit cône tronqué.
2. Dispositif suivant la revendication 1, dans lequel le rapport des diamètres du sommet à la base du cône tronqué est compris dans l'intervalle de 1:2 à 1:4, et le rapport de la hauteur au diamètre de la base est compris dans l'intervalle de 1:1 à 1:4.
3. Dispositif suivant la revendication 1 ou 2, dans lequel le cône tronqué possède une base convexe.
4. Dispositif suivant l'une quelconque des revendications précédentes, dans lequel la substance est physiquement active.
5. Dispositif suivant l'une quelconque des revendications précédentes, dans lequel l'activité est une activité germicide, pharmaceutique ou évitant ou réduisant les odeurs dans le, ou provenant du, milieu fluide.
6. Dispositif suivant l'une quelconque des revendications précédentes, dans lequel l'activité est une activité germicide, pharmaceutique ou évitant ou réduisant les odeurs dans le, ou provenant du, milieu fluide.
7. Bol destiné à l'administration orale dans le reticulum ou le rumen d'un mammifère ruminant, ledit bol étant retenu dans ledit rumen ou reticulum et libérant un ou plusieurs agents actifs dans le milieu du dudit rumen ou reticulum à une vitesse pratiquement constante pendant une longue période, qui comprend un ou plusieurs dispositifs suivant l'une quelconque des revendications précédentes, le ou les agents actifs étant répartis de manière homogène dans une matrice et présents sous forme d'un ou plusieurs cônes nettement tronqués au moyen d'une paroi imperméable sur la base et le côté du ou des cônes tronqués.
8. Bol suivant la revendication 7, comprenant l'agent actif présent dans plusieurs cavités en forme de cônes tronqués, dans plusieurs cylindres plats ou disques montés dans un support de forme cylindrique allongée et espacés pour permettre l'accès du sommet desdits cônes tronqués au milieu du rumen ou du reticulum, ledit support ayant une patte flexible et résiliente fixée, pouvant être maintenue sous une configuration enroulée autour dudit cylindre allongé par des moyens de contention qui libèrent ladite patte une fois dans le milieu du reticulum ou du rumen.
9. Bol suivant la revendication 8, dans lequel l'agent actif est le morantel ou un de ses sels pharmaceutiquement acceptables, dans une matrice polymérique.
10. Comprimé destiné à l'administration orale à un mammifère, qui libère une substance pharmaceutiquement active dans le fluide du tractus gastro-intestinal dudit mammifère à une vitesse constante pendant un temps notable, qui comprend un dispositif suivant l'une quelconque des revendications 1 à 6 comprenant la substance répartie de manière homogène, avec ou sans un ou plusieurs diluants

pharmaceutiquement acceptables, et présente sous forme d'un cône nettement tronqué au moyen d'un revêtement ou d'une paroi imperméable sur la base et le côté dudit cône tronqué.

- 5 11. Comprimé suivant la revendication 10, dans lequel la substance est maintenue au moyen d'un revêtement.
- 10 12. Comprimé suivant la revendication 10 ou 11, dans lequel la substance est un agent anti-hypertenseur, un anxiolytique, un bronchodilatateur ou un agent abaissant la teneur sanguine en glucose.
- 15 13. Comprimé suivant les revendications 10 à 12, dans lequel la substance est la prazosine, la trimazosine, la doxazosine, l'hydroxyzine, la sertraline, le piritbutérol ou le glipizide.
- 20 14. Presse à comprimés à un seul poste ou à plusieurs postes, destinée à être utilisée dans la production de comprimés sous forme de cônes nettement tronqués, qui, à chaque poste, comprend
  - (a) un poinçon inférieur classique, circulaire et plat ou convexe;
  - (b) une matrice circulaire classique; et
  - (c) un poinçon supérieur correspondant, ayant une cavité qui est sous forme d'un cône nettement tronqué.
- 25 15. Presse à comprimés suivant la revendication 14, dans laquelle le côté de la cavité en forme de cône est de forme concave.
- 30 16. Presse à comprimés suivant la revendication 14 ou 15, dans laquelle le rapport des diamètres du sommet et de la base du cône tronqué est compris dans l'intervalle de 1:2 à 1:4 et le rapport de la hauteur au diamètre de la base est compris dans l'intervalle de 1:1 à 1:4.
- 35 17. Appareil pour éliminer le revêtement de l'extrémité de plus petit diamètre d'un comprimé totalement enrobé qui est sous la forme d'un premier cône nettement tronqué, qui comprend
  - (a) une plaque horizontale mobile contenant plusieurs perforations sous forme d'un second cône équilangèle fortement tronqué, moins haut, ayant son plus grand diamètre au sommet de la plaque et non supérieur au plus grand diamètre dudit premier cône tronqué, et son plus petit diamètre au fond de la plaque et plus grand que le plus petit diamètre dudit premier cône tronqué;
  - (b) des moyens pour placer lesdits comprimés totalement enrobés dans lesdites perforations;
  - (c) un dispositif stationnaire de support audessus de ladite plaque mobile pour maintenir en place les comprimés installés;
  - (d) un dispositif stationnaire de meulage au-dessous du plan de ladite plaque, espacé de manière à éliminer l'enrobage de l'extrémité de plus petit diamètre desdits comprimés placés sur le support;
  - (e) un dispositif d'éjection des comprimés finis.
- 40 18. Procédé pour la préparation d'un comprimé suivant la revendication 10, qui comprend les étapes consistant:
  - (a) à préparer des comprimés non enrobés sous forme d'un cône nettement tronqué dans une presse à comprimés à un seul post ou à plusieurs postes comprenant un poinçon inférieur classique circulaire et plat ou convexe; une matrice centrale circulaire classique correspondante;
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et un poinçon supérieur correspondant ayant une cavité qui est sous forme d'un cône nettement tronqué;

(b) à enrober totalement lesdits comprimés non enrobés avec un enrobage imperméable par des moyens classiques;

(c) à éliminer l'enrobage de l'extrémité de plus petit diamètre des comprimés totalement enrobés au moyen d'un appareil comprenant une plaque horizontale mobile ayant des perforations d'une forme et d'un diamètre permettant d'installer lesdits comprimés avec la plus petite extrémité au-dessous du plan de la plaque; un dispositif pour installer lesdits comprimés totalement enrobés dans lesdites perforations; un dispositif de support stationnaire au-dessus de ladite plaque mobile pour maintenir en place lesdits comprimés; un dispositif de meulage stationnaire au-dessous du plan de ladite plaque, espacé de manière à éliminer l'enrobage de l'extrémité de plus petit diamètre des comprimés totalement enrobés; et un dispositif pour l'éjection des comprimés finis.

19. Procédé suivant la revendication 18, dans lequel, dans l'étape (a) le poinçon inférieur est convexe.

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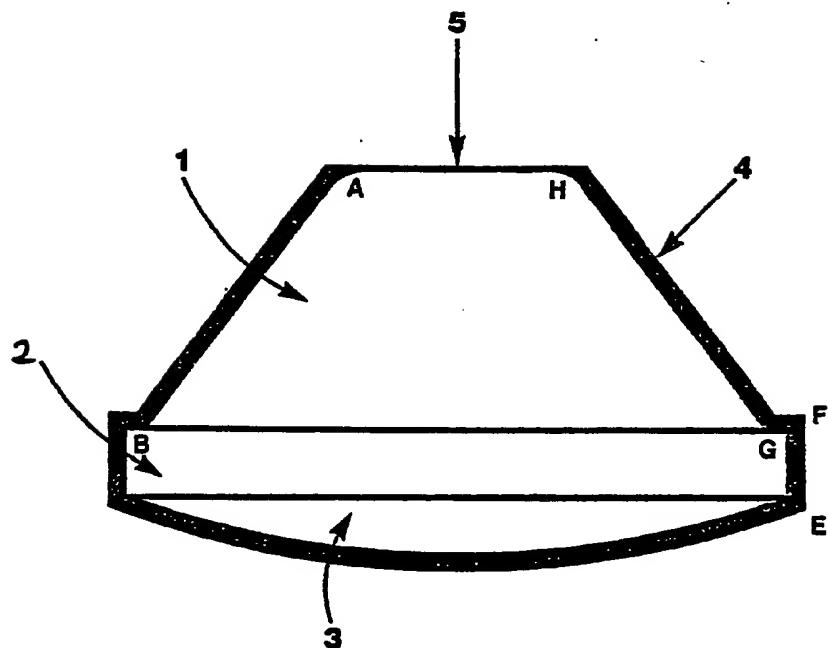
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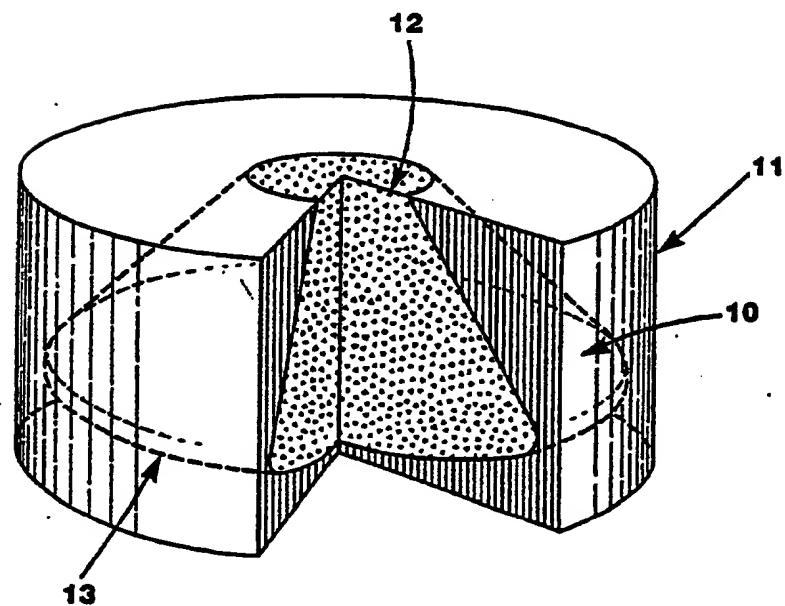
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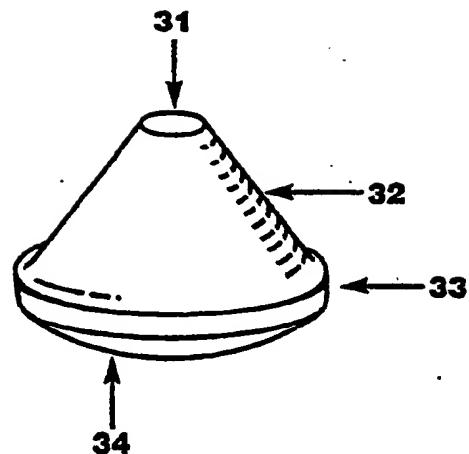


**Figure 1**

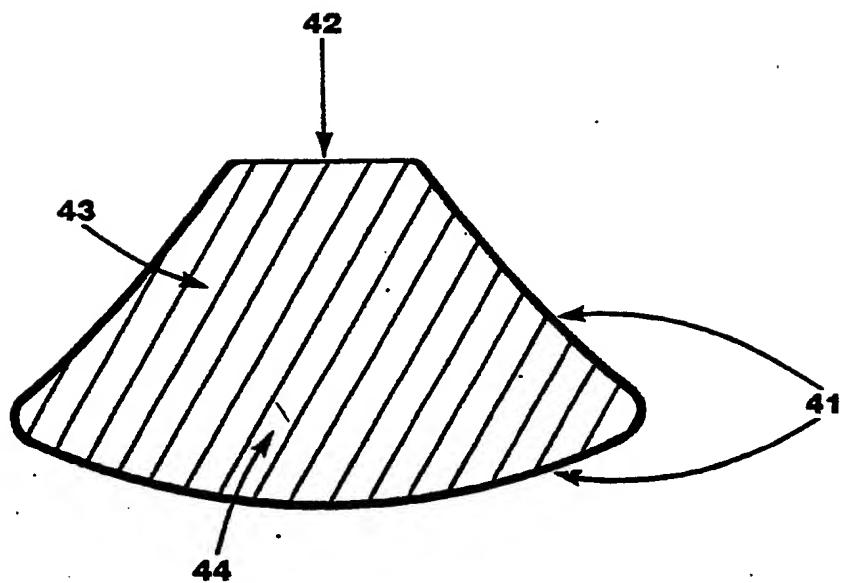


**Figure 2**

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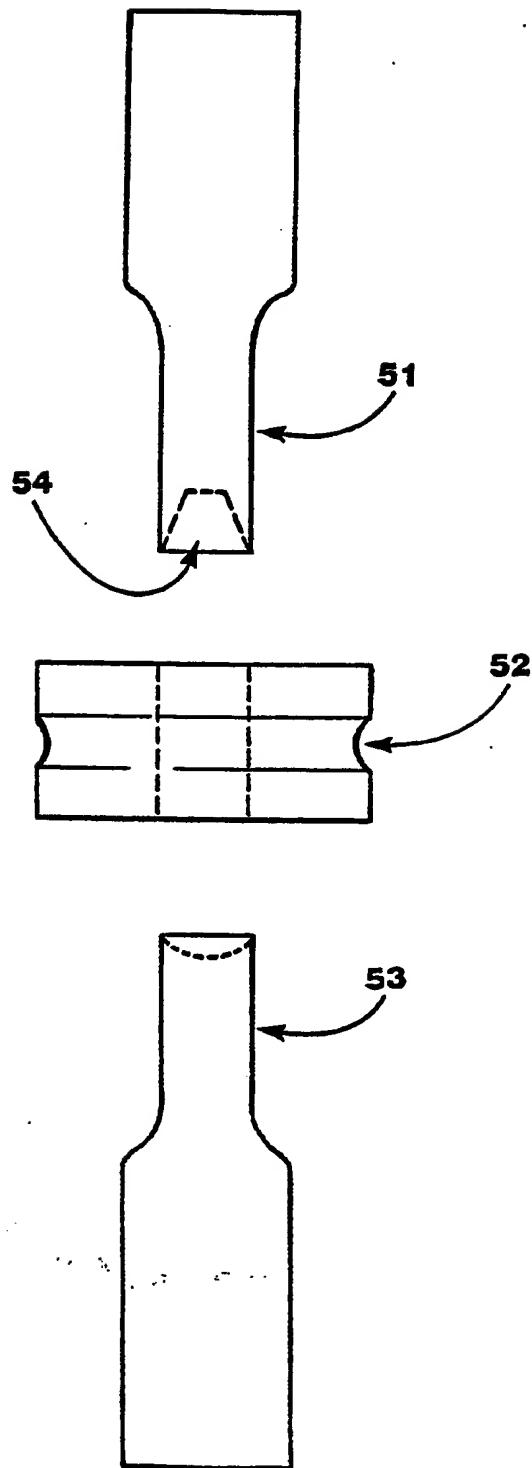


**Figure 3**



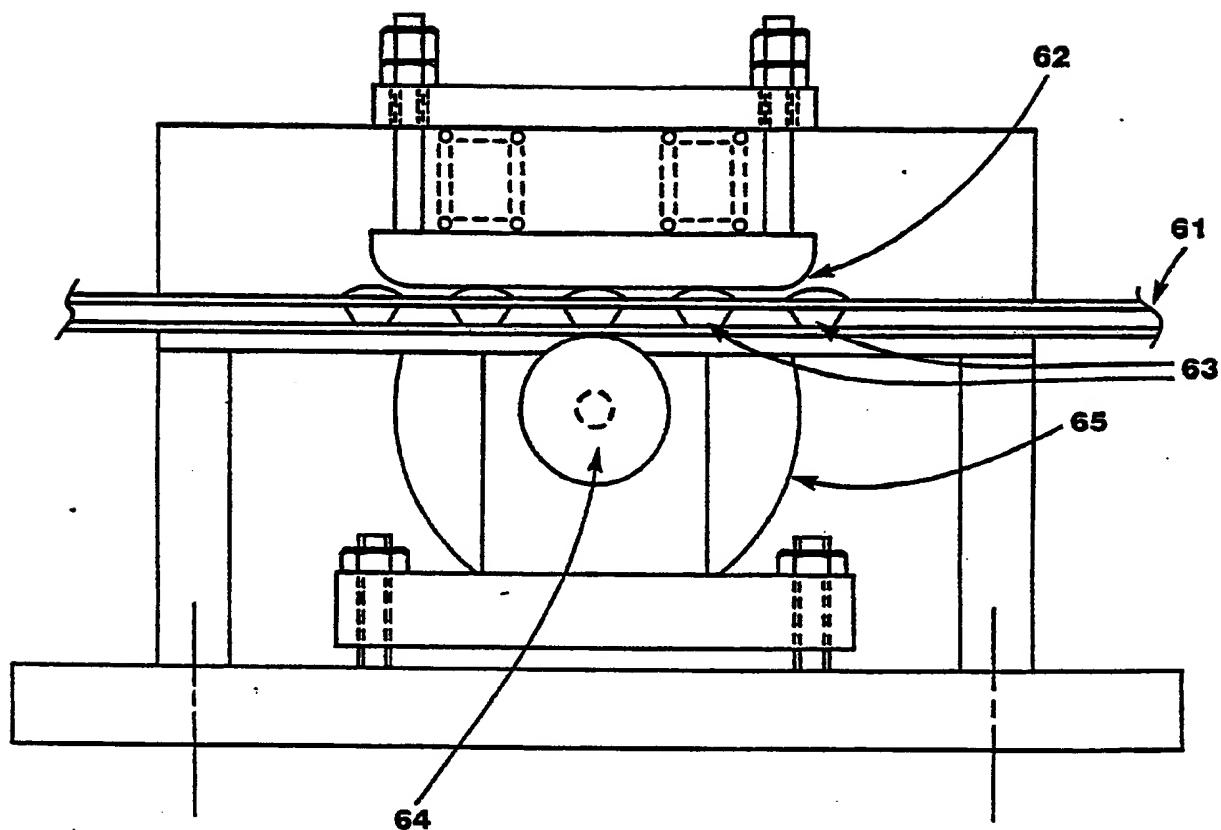
**Figure 4**

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**Figure 5**

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**Figure 6**

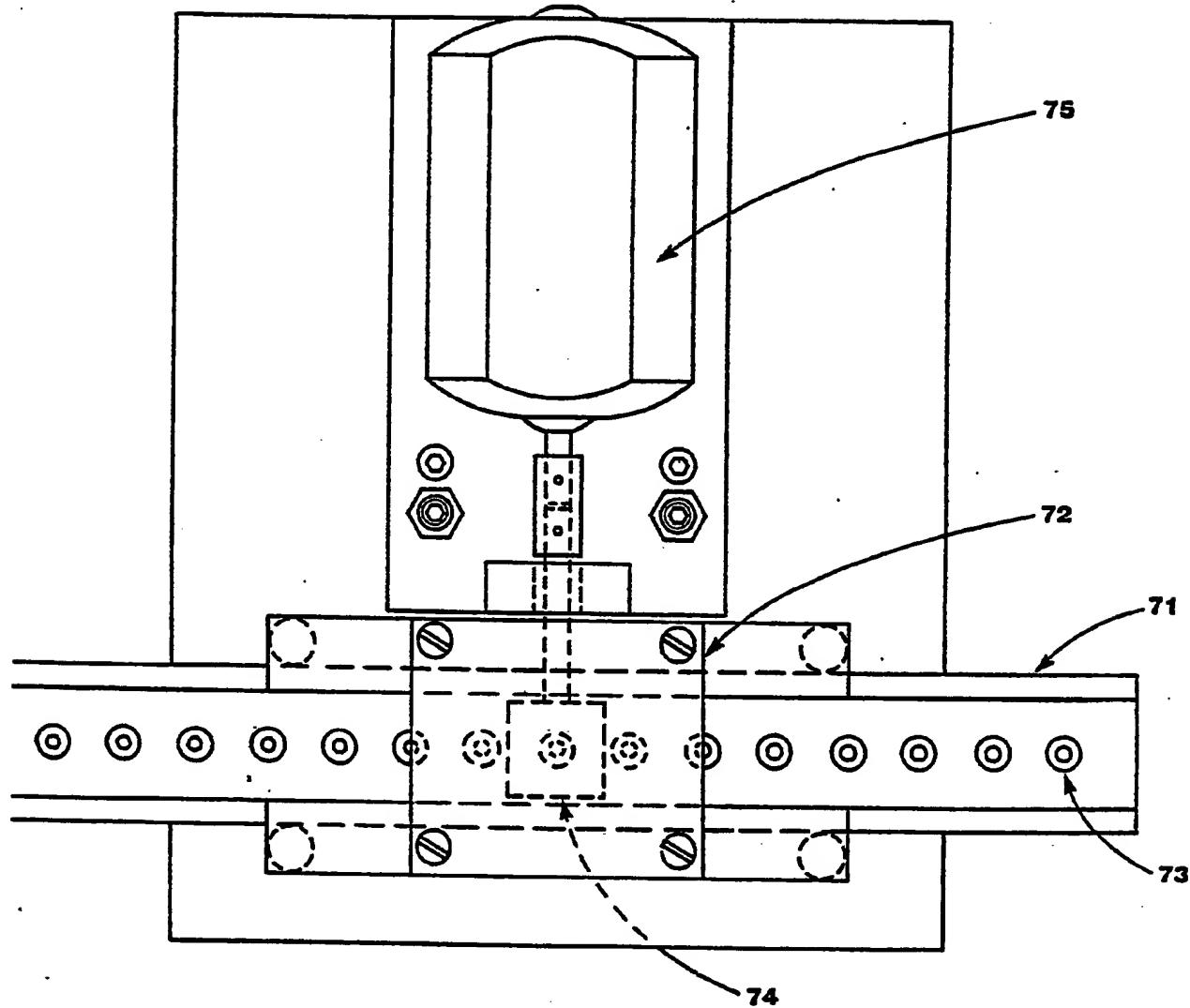
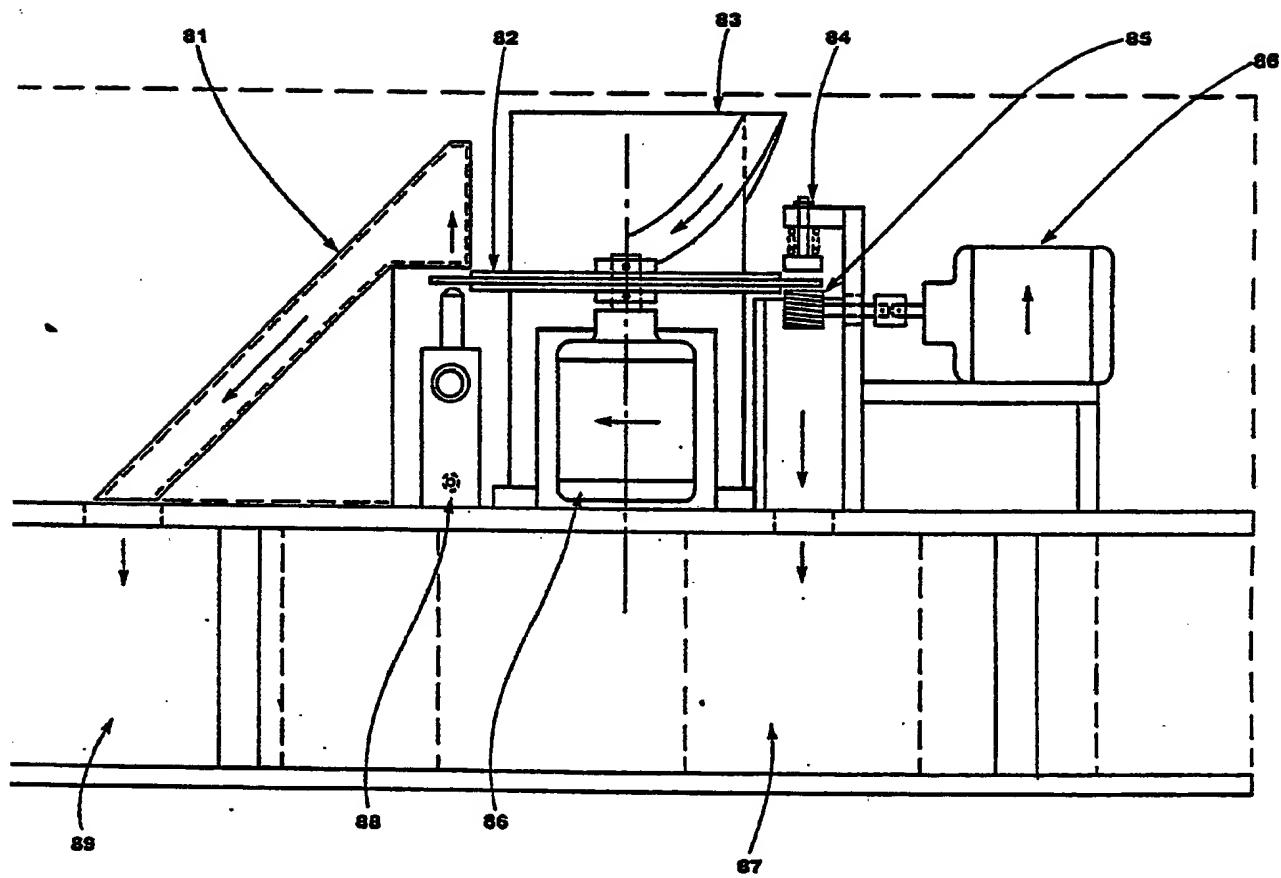


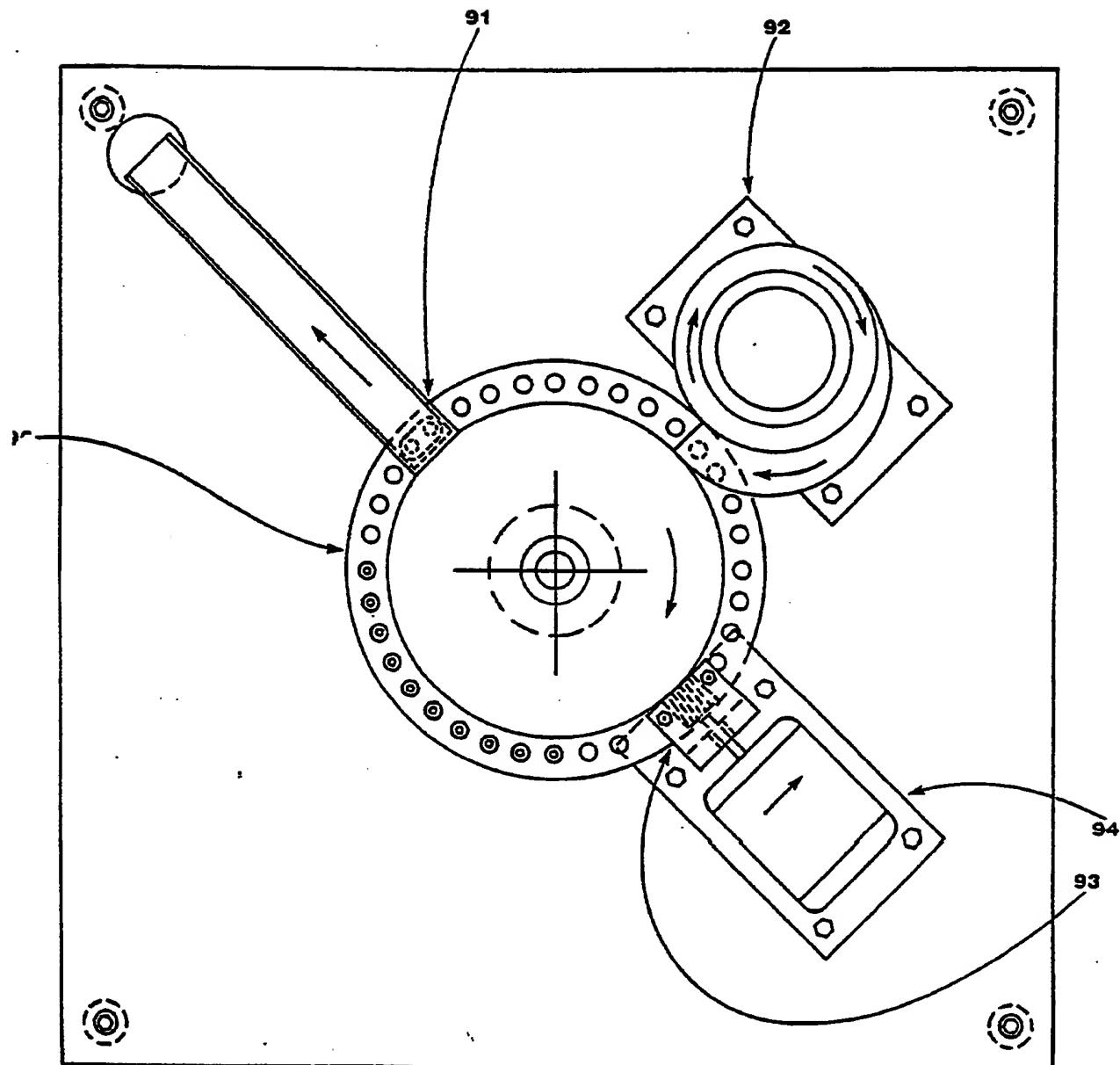
Figure 7

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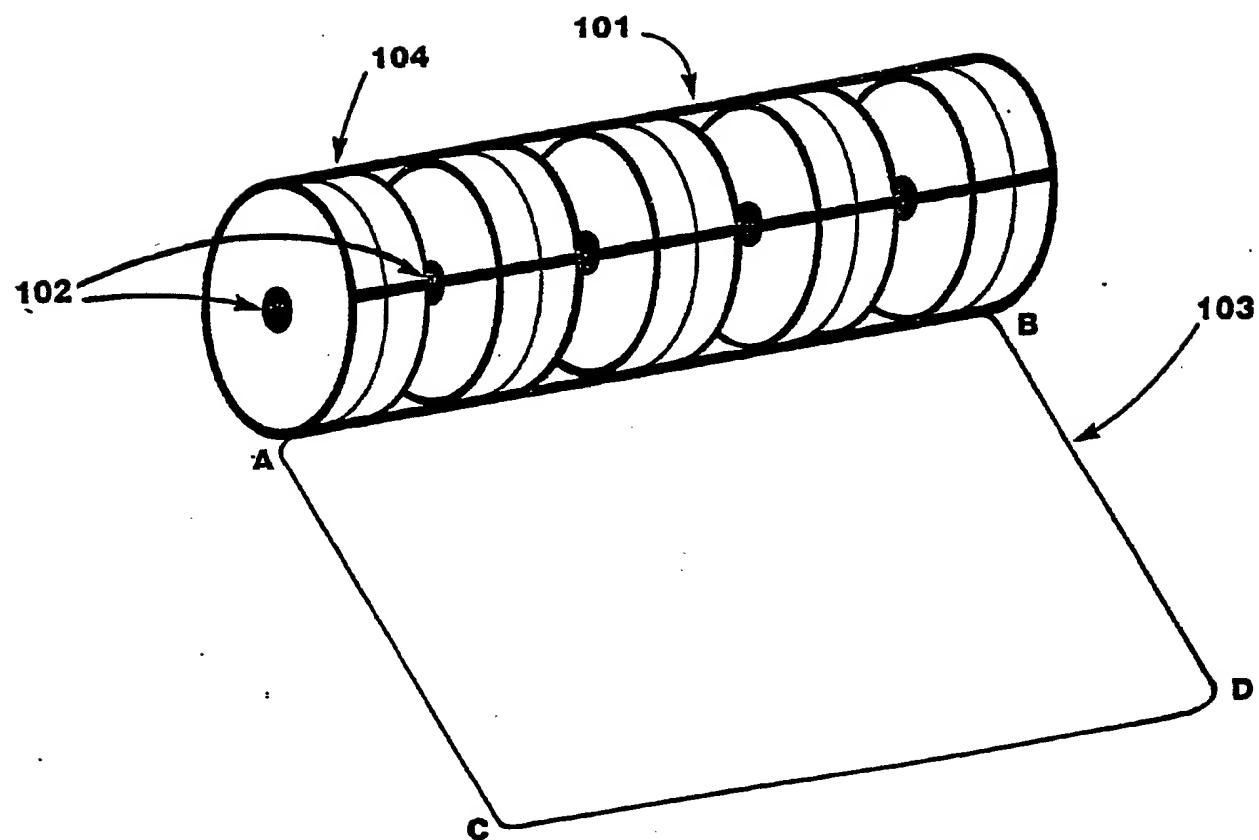
**Figure 8**

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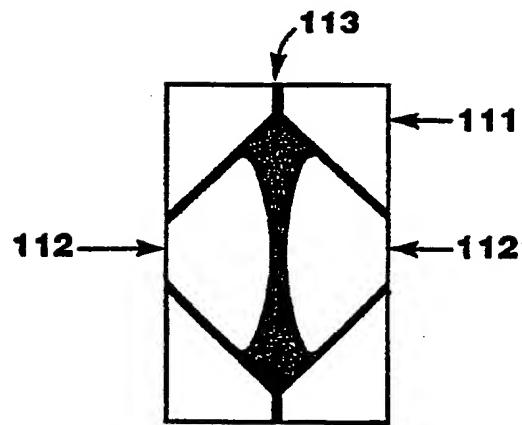
**Figure 9**

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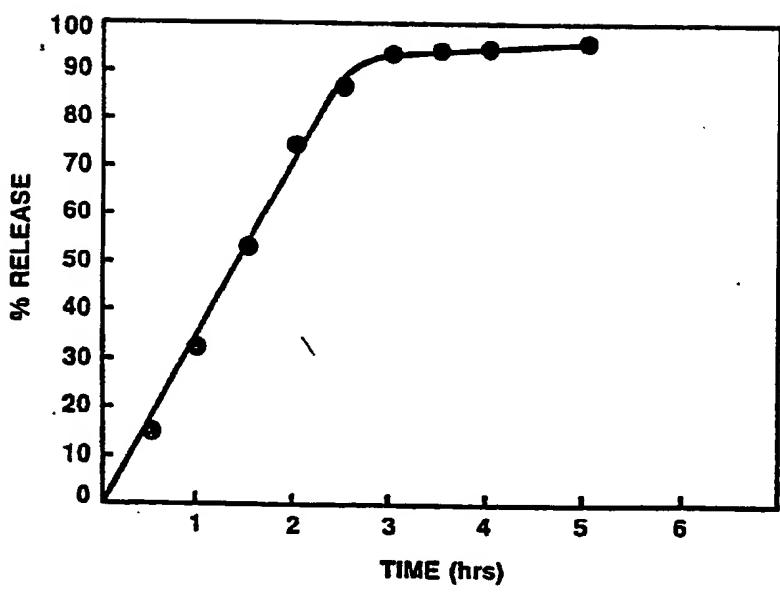


**Figure 10**

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**Figure 11**



**Figure 12**

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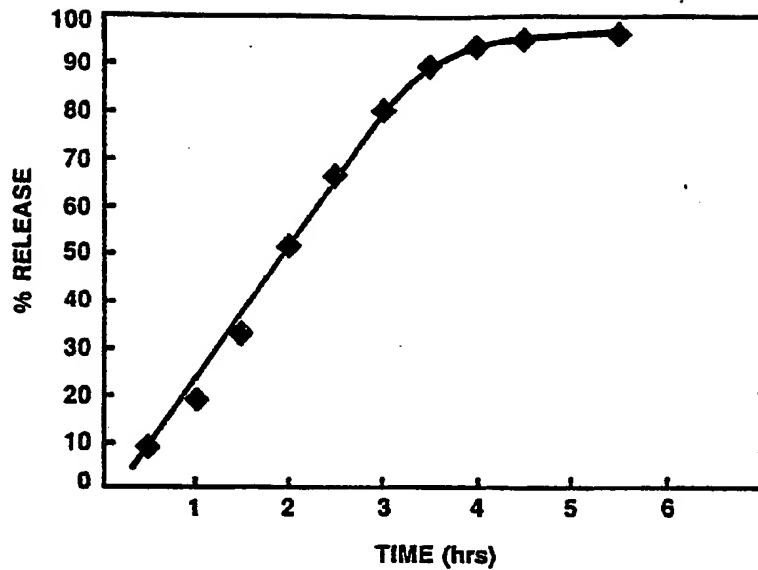


Figure 13

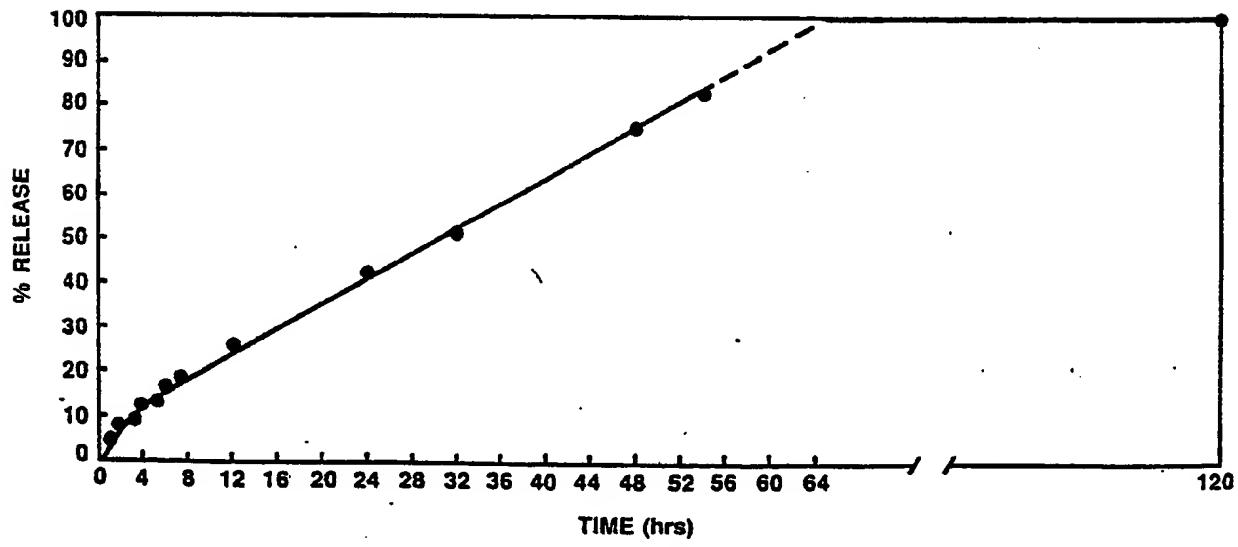


Figure 14

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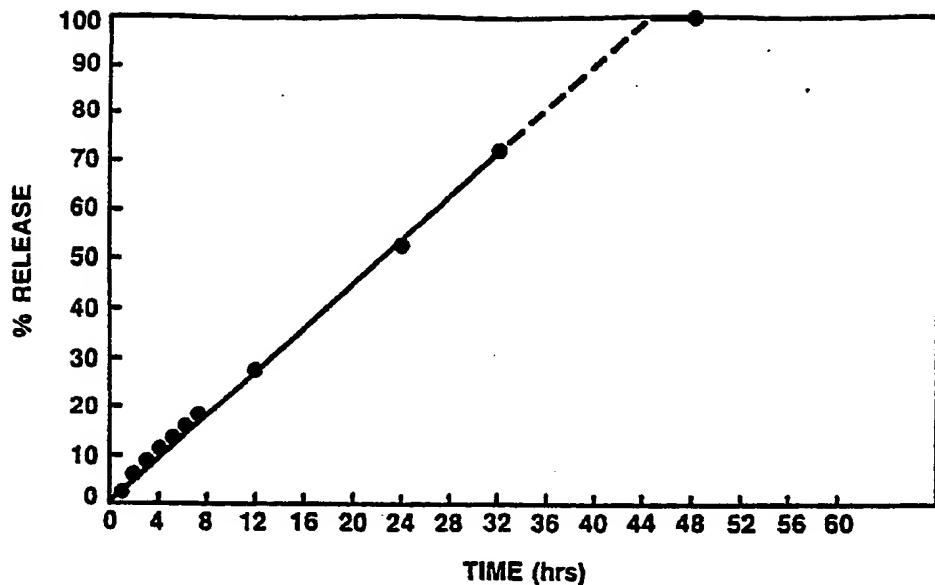


Figure 15

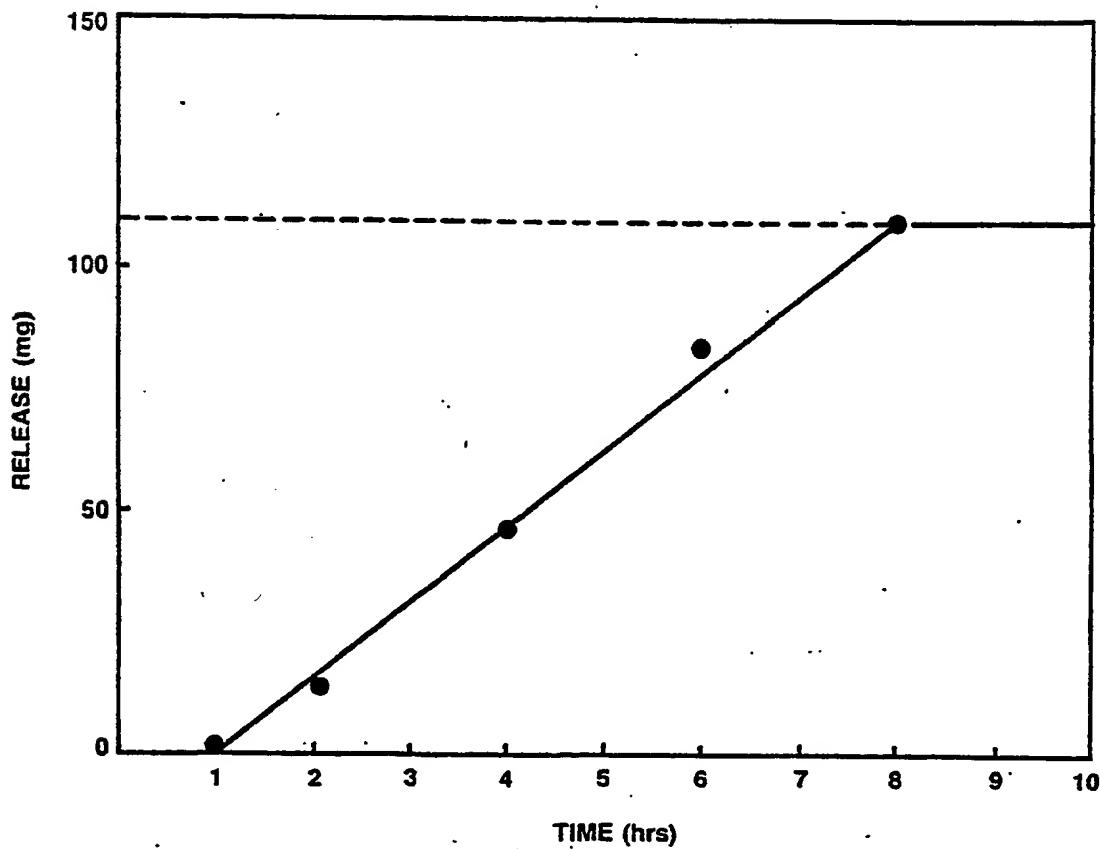


Figure 16